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(54) **Pharmaceutical and dietary composition comprising gamma-linolenic acids.**

(57) **Compositions and use of γ -linolenic acids and related materials in association with zinc and/or β -lactam antibiotics to treat schizophrenia, obesity, menstrual disorders, skin disorders and other conditions.**

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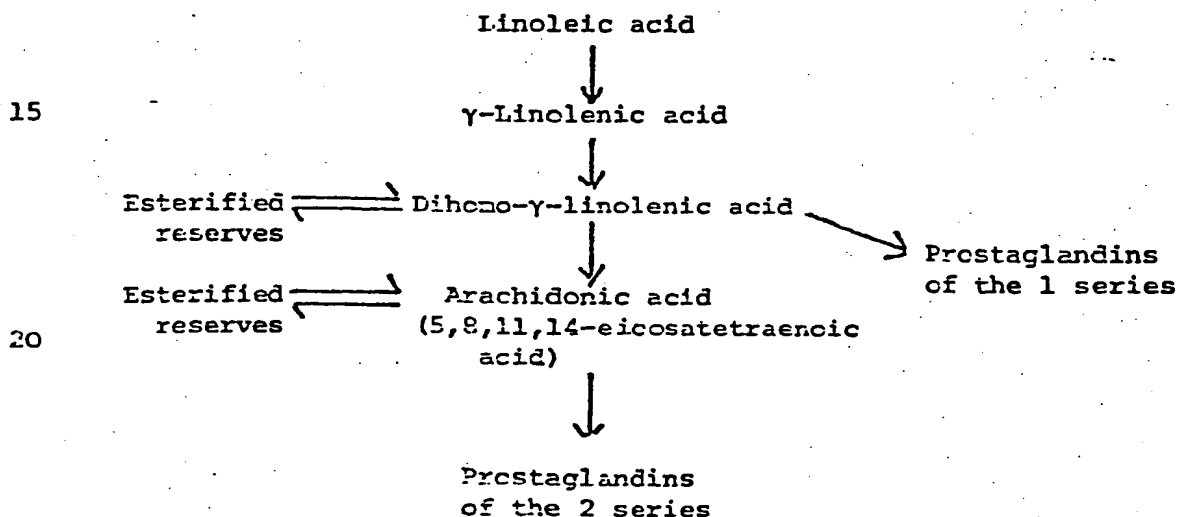
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"PHARMACEUTICAL AND DIETARY COMPOSITION"

This invention relates to compositions for the treatment of various diseases and disorders primarily, but not exclusively, in the field of human medicine.

Considerable interest has been shown in recent years in the use of prostaglandin (PG) precursors in medicine.

For various reasons it is not practical to administer naturally-occurring prostaglandins such as PGE 1 and PGE 2 to patients. Consequently, considerable attention has focussed on the use of prostaglandin precursors including linoleic acid (9,12-octadecadienoic acid), γ -linolenic acid (6,9,12-octadecatrienoic acid) and dihomogamma-linolenic acid (5,8,11-eicosatrienoic acid), conversion in the body being believed to be as follows:



Prior art within this general area includes the following

patents and papers.

(i) U.S. Patents Nos. 3 993 775 (issued November 23rd, 1976) and 4 058 594 (issued November 15th, 1977) of John Williams, which describe a method of providing an immuno-suppressive effect in a patient undergoing organ or tissue transplant or suffering from multiple sclerosis comprising administration of a daily dosage of from 5 mg to 3 g of γ -linolenic acid or dihomogamma-linolenic acid or a functional derivative thereof.

(ii) British Patent Specification No. 1 082 624, published September 6th, 1967, (Calmic Limited), which discloses effectiveness of γ -linolenic acid in the treatment of vascular diseases.

(iii) McCormack, Neil and Sim (The Lancet, page 308, September 3rd, 1977), who describe preliminary work on the use of an oil containing a mixture of linoleic acid and γ -linolenic acid (as triglycerides) in the treatment of rheumatoid arthritis.

(iv) Sim and McCraw (Thrombosis Research Volume 10, pages 385-397, 1977), who describe activity of the methyl esters of γ -linolenic acid and dihomogamma-linolenic acid in vitro and in vivo on blood platelet function in non-human primates and in man.

The present inventor has discovered a number of new applications of γ -linolenic acid and dihomogamma-linolenic acid in therapy, in conjunction with zinc and/or β -lactam antibiotics. These are now described in turn.

SCHIZOPHRENIA

In the Lancet, page 936, April 30, 1977 the present inventor has suggested that schizophrenia is a prostaglandin deficiency disease. Schizophrenia is not a disorder which would suggest the use of immuno-suppressive drugs. The specific suggestion was made that arachidonic acid, known to be a precursor of prostaglandins of the 2 series should alleviate schizophrenia.

As a result of further research, the present inventor now believes that schizophrenia is due not to a deficiency of 2 series PG's but rather to a deficiency of PGE 1 and other PG's of the 1 series, of which arachidonic acid is not a precursor, or an imbalance in the normal ratio of 1 series and 2 series PG's.

This has led to the realization that the materials which should be used to stimulate the natural production of 1 series PG's in the treatment of schizophrenia should include γ -linolenic acid and/or dihomio- γ -linolenic acid, either or both of which may be used in association with linoleic acid and if desired other fat acids. Although these substances are 2 series PG precursors (via arachidonic acid) as well as 1 series PG precursors, this is not deleterious to their use, although one may require to use relatively higher amounts of precursors than would be the case if only 1 series PG's were being biosynthesized.

SKIN DISORDERS

A further area where the administration of 1 series PG precursors is indicated is in the treatment of psoriasis and other human skin disorders such as acne, dandruff, eczema and hair loss (other than that due to inherited male pattern baldness).

The physiological basis for these treatments is not understood in detail but it is believed by the present inventor that conditions such as psoriasis, dandruff, eczema and hair loss are related to each other by common, or at least related, defects in 1 series PG precursor metabolism, expressing themselves in various ways in different individuals. Experimental evidence of a relation is discussed below in the section on veterinary application of the invention. Acne stands more on its own as a condition in particular of young males, but is certainly related to the metabolism of fatty materials in the skin.

OBESITY

A current technique for the treatment of obesity involves the administration of linoleic acid, generally in the form of vegetable oils such as sunflower oil and/or corn oil. In order to be effective, these current dietary approaches to the treatment of obesity require the intake of other fats in the diet to be substantially reduced. In the body, linoleic acid is converted as described earlier and the present inventor believes that the beneficial effect of administration of linoleic acid is due to enhancement of 1 series PG production and in particular of PGE 1,

this substance causing a metabolic shift increasing appetite and reducing weight. However, the presence of other fats in the diet interferes with the conversion of linoleic acid to γ -linolenic acid and thus reduces the effectiveness of the treatment.

5 What is now proposed is administration of materials including γ -linolenic acid and/or dihomo- γ -linolenic acid or derivatives, as effective in the treatment of obesity, even when other fats are present in the diet.

MENSTRUAL DISORDERS

10 Menstrual disorders are not uncommon and while they do not usually require clinical treatment they are often a cause of distress or discomfort. Such disorders include: extended periods of blood loss, sometimes for as long as 9 days or more, especially when using intra-uterine contraceptive devices; excessive blood loss during menstrus, which is again often associated with the use
15 of intra-uterine contraceptive devices; so-called "period pains"; premenstrual swelling associated with excessive fluid retention; and irregular menstrual cycle lengths.

The present inventor has now surprisingly found that the administration of materials including γ -linolenic acid and/or
20 dihomo- γ -linolenic acid or derivatives causes a significant reduction in some or all of the above mentioned menstrual disorders.

In tests which have been effected by the present inventor, it has been found that women previously exhibiting excessive periods of blood loss during menstrus experienced a reduction in
25 this period to 3 to 5 days on treatment according to the invention. In addition these tests have shown that a reduction in amount of blood loss, period pains and premenstrual swelling and a stabilisation of menstrual cycle lengths, may be achieved.

30 The physiological explanation for the efficacy of the treatment is not fully understood. However, whilst not wishing to be bound by theoretical considerations, the inventor has noted that these types of menstrual disorders are often associated with obesity, which appears in at least some subjects to be due to a deficiency in essential fatty acids.

USE OF ZINC

As has been mentioned above, γ -linolenic acid and dihomogamma-linolenic acid function as precursors for both 1 and 2 series-PG's. The present inventor specifically believes it advantageous if the biosynthesis of 1 series PG's can be effected preferentially to that of 2 series PG's in conditions, not merely schizophrenia and the other applications discussed in some detail herein, but also the conditions treated according to the prior art discussed in which 1 series PG imbalances or lack need to be corrected.

Without restriction to the theory, the present inventor believes that zinc tends to stimulate the biosynthesis of 1 series PG's and specifically that it potentiates mobilisation of esterified reserves of dihomogamma-linolenic acid. This enables one to use zinc conjointly with γ -linolenic acid and/or dihomogamma-linolenic acid. The presence of arachidonic acid or any other material tending to oppose the PG 1 enhancing effect is to be avoided.

USE OF β -LACTAM ANTIBIOTICS

The use of γ -linolenic or other acids and derivatives with β -lactam antibiotics is also valuable. The present inventor believes that the reason for the effectiveness of the antibiotics is that, as he believes with zinc, they enhance utilisation of ester reserves of dihomogamma-linolenic acid. Whether or not this is so, and no restriction to the theory is intended, zinc and antibiotics do appear to have parallel effects in treating all the conditions when used with the γ -linolenic or other acids and derivatives.

It is also possible and has been found valuable to use both zinc and β -lactam antibiotic conjointly with the γ -linolenic acid, dihomogamma-linolenic acid or derivatives.

FORMAL STATEMENT OF INVENTION

The invention thus specifically provides a pharmaceutical or dietary composition comprising (a) γ -linolenic acid or physiologically functional derivative thereof and/or dihomogamma-linolenic acid or physiologically functional derivative thereof and a conjoint amount of (b) physiologically assimilable zinc

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and/or (c) a β -lactam antibiotic, alone or in an acceptable pharmaceutical or dietary vehicle.

Alternatively, if it is not desired to have compositions comprising both the antibiotic and/or zinc and the γ -linolenic or other acid or derivative, packs may be prepared comprising the active materials presented for separate administration, or two together and one separately, in the appropriate relative amounts, and such packs are within the purview of the invention.

AMOUNTS OF γ -LINOLENIC AND OTHER ACIDS

A preferred daily dosage for an adult (weight ca 75 kg) is from 0.05 or 0.1 up to 1, 2, 5 or even 10 g as required of γ -linolenic acid or equivalent weight (calculated as γ -linolenic acid) of physiologically functional derivative thereof. Amounts may in particular be 0.1 to 1.0 g daily. In place of, or in addition to, γ -linolenic acid, one may use dihomogamma-linolenic acid or a physiologically functional derivative thereof, in amounts equivalent in molar terms to γ -linolenic acid and calculated as such. This dosage can for example be taken as a single dose or divided into 2, 3, or 4 subdivisions thereof as convenient.

FORMS AND SOURCES OF γ -LINOLENIC AND OTHER ACIDS

Convenient physiologically functional derivatives of γ -linolenic acid and dihomogamma-linolenic acid for use for all the purposes described include the $C_1 - C_4$ alkyl (e.g. methyl and ethyl) esters and the glycerides of the acids.

If desired, pharmaceutical compositions may be produced for use in the invention by associating natural or synthetic γ -linolenic acid (or a physiologically functional derivative thereof) and/or dihomogamma-linolenic acid (or a physiologically functional derivative thereof) as such, with an acceptable pharmaceutical vehicle. It will however generally be convenient to incorporate the γ -linolenic acid into compositions in the form of an available oil having a high γ -linolenic acid content.

At the present time known natural sources of oils having a high γ -linolenic acid content are few (there are no known natural sources of significant amounts of dihomogamma-linolenic acid).

One source of oils currently available is the seed of Evening Primrose species such as Oenothera biennis L. and Oenothera lamarckiana, the oil extract therefrom containing γ -linolenic acid and linoleic acid in the form of their glycerides together with other glycerides. Another source of γ -linolenic acid is the seed of Borage species such as Borago officinalis which, though its current yield per acre is low, provides a richer source of γ -linolenic acid than Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The seed oil extracts referred to above can be used as such or can if desired be fractionated to yield an oily composition containing the triglycerides of γ -linolenic acid and linoleic acid as the only fatty acid components, the γ -linolenic acid content being a major proportion. Seed oil extracts appear to have a stabilising effect upon any dihomogamma-linolenic acid or physiologically functional derivative thereof incorporated therein.

AMOUNTS AND FORMS OF ZINC

Based on present evidence, a suitable daily dosage of zinc for an adult (weight ca 75 kg) is 2.5-800 mg preferably 10-200 mg and advantageously 10-80 mg zinc daily, with γ -linolenic acid or other acid or equivalent in the amounts previously discussed. The 10-80 mg zinc is approximately 0.125-1.0 mg/kg adult body weight. In view of the conjoint effect of the zinc preferred amount of γ -linolenic or other acid or equivalent are less than when zinc is not present, advantageously 0.1 to 1.0 g daily. As before the dosage can be taken as a single dose or divided into 2, 3 or 4 subdivisions thereof.

The zinc should be administered in a form in which it is readily taken up in vivo. Ordinarily this will indicate the use of a zinc salt of a mineral or organic acid, said salt being physiologically acceptable at the given dosage. Some zinc salts which would be contra-indicated at higher dosages may be satisfactory for present purposes at the dosages indicated above. Useful salts include zinc sulphate and zinc gluconate and in particular zinc oleate, γ -linolenate and dihomogamma-linolenate, and zinc oxide may

also be employed. It is also possible to administer the zinc in chelated form. In any event, the preferred amounts of zinc are as stated above (the quantities given being calculated as zinc metal).

KINDS AND AMOUNTS OF ANTIBIOTIC

5 β -lactam antibiotics which may be used according to the present invention, are conveniently any of the known penicillin and cephalosporin antibiotics (including semi-synthetic antibiotics) such as, for example, penicillin G, penicillin N, penicillin V, cephalixin, cephalothin, ampicillin, amoxycillin, cloxacillin and
10 cephalogylcin. Any of these may be used in the form of their physiologically functional non-toxic derivatives, for example alkali metal salts e.g. sodium and potassium salts, and salts with organic bases, and reference to an antibiotic herein (including the claims) includes reference to such derivatives.

15 The antibiotic is preferably administered in daily dosages of for example 0.5 to 3.0 g per day in patients of average weight. Such daily dosages may conveniently be divided into for example, two, three or four equal doses to be administered two, three of four times daily respectively.

20 SPECIFIC INDICATIONS IN SCHIZOPHRENIA

 In severely disturbed patients it may be desirable to additionally administer conventional tranquillizers in addition to regular treatment with the compositions of the invention, but this is only required when such patients experience extreme agitation,
25 insomnia or hallucinations.

 The use of penicillins in the long term treatment of schizophrenia is especially desirable in view of the known relative absence of side effects of these drugs. Thus, penicillin has been administered for many years to patients having rheumatic heart
30 disease in order to prevent streptococcal infections, and there is virtually no evidence of long term toxicity.

 Care should of course be taken to ensure that the patient is not allergic to the drug of choice. With respect to the known ability of penicillins to produce reactions in some patients due
35 to penicillin hypersensitivity, there is evidence to suggest that

schizophrenics have a reduced incidence of allergic reactions and more particularly of penicillin hypersensitivity. Thus, the problem, usually associated with penicillin antibiotic therapy, of hypersensitization in a small number of patients, is not quite
5 so important in the treatment of schizophrenia using penicillins.

A valuable benefit of the present invention is that the hitherto extensively used chemotherapeutic agents for schizophrenia have been associated with a tranquillizing activity, with the result that the use of these drugs in therapy is combined with an often
10 undesired heavy sedation of the patient. Also such drugs may be responsible for the production of irreversible damages in up to 70% of patients to those parts of the brain which control movement. Avoidance or substantial avoidance of the use of these drugs is thus of great value.

15 DIETARY COMPOSITIONS

The invention is chiefly described in terms of pharmaceutical compositions, but it will be understood that the γ -linolenic and other acids, being in the nature of dietary supplements, could if available at an economic price be incorporated in a dietary margarine or other foodstuff; such foodstuffs, referred to herein as dietary
20 compositions, are within the purview of the invention.

VETERINARY APPLICATIONS

It will be understood that where a disorder of the kind calling for treatment in animals arises, the invention while described
25 primarily in terms of human medicine and treatment is equally applicable in the veterinary field.

Thus for example domestic cats have an unusual dietary requirement in essential fatty acids, being apparently unable to convert linoleic acid to γ -linolenic acid and dihomio- γ -linolenic acid to arachidonic acid. They are liable to a group of related
30 skin conditions with hair loss, dandruff, scaling, pruritis, easy breakdown of the skin with rubbing or scratching, and defective healing, all of which can also be produced experimentally by an EPA (essential fatty acid) deficient diet, evidencing their related
35 nature. Similar conditions can be produced experimentally in other

animals, with skin lesions similar to eczema and psoriasis. Feeding of γ - or dihom- γ -linolenic acid is effective in reversing the conditions, including, perhaps surprisingly, those in cats. This indicates, in view of the arachidonic acid block, that the conditions are indeed, as the present inventor believes also for the human skin conditions discussed above, related to 1 series PG deficiencies. The spontaneous conditions observed in cats are for example relived by giving 0.5 g of Oenothera oil and zinc 20 mg as sulphate, per day, five days a week.

10 PHARMACEUTICAL PRESENTATION

The compositions according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1 082 624 and in any case known generally according to the type of preparation. Thus for example tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required.

Advantageously a preservative such as α -tocopherol is incorporated into the preparations. α -Tocopherol in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following Examples serve to illustrate pharmaceutical compositions according to the invention:

30 EXAMPLES

Pharmaceutical compositions containing a unit dose of an oil extract from the seeds of Oenothera biennis L. optionally with methyl dihom- γ -linolenate and with zinc in suitable form and/or penicillin V are prepared by encapsulation of the natural oil in

soft gelatin capsules manufactured by known methods.

The oil is extracted from the seeds by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

5 Fractionation of a typical sample of this oil shows a yield of 97.0% oil in the form of methyl esters, with the relative proportions:

	Palmitate	6.15
	Stearate	1.6
10	Oleate	10.15
	Linoleate	72.6
	γ -Linolenate	8.9

As preservative, α -tocopherol is added to the oil in a concentration of 0.1%.

15 Gelatin capsules containing oil extracts prepared as described above, each having the following contents of active ingredients (0.5 g oil extract = ca 0.045 g γ -linolenic acid), are prepared in conventional fashion. The zinc may conveniently be incorporated as zinc oleate made by the method disclosed in Monatschrift 42 287
20 (1921), and similar methods may be applied to make for example zinc γ -linolenate if desired.

EXAMPLE 1

	Oil extract	0.5 g
	Zinc sulphate	10 mg

25 Two capsules may be administered thrice daily in the treatment of schizophrenia or menstrual disorders, giving a daily dose of γ -linolenic acid of ca 0.27 g. Similar capsules with 20 mg zinc sulphate may be administered in the treatment of acne, psoriasis, eczema, dandruff and loss of hair, or of obesity.

EXAMPLE 2

	Oil extract	0.5 g
	Methyl dihomog- γ -linolenate	10 mg
	Zinc sulphate	10 mg

30 Two capsules may be administered thrice daily in the treatment of
35 schizophrenia.

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EXAMPLE 3

Oil extract	0.5 g
Penicillin V	0.25 g

5 Two capsules may be administered thrice daily in the treatment of schizophrenia.

EXAMPLE 4

Oil extract	0.5 g
Penicillin V	0.25 g
Zinc sulphate	10 mg

10 Two capsules may be administered thrice daily in the treatment of schizophrenia.

EXAMPLE 5

Oil extract	0.5 g
Methyl dihomog- γ -linolenate	10 mg
Penicillin V	0.25 g
Zinc sulphate	10 mg

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Two capsules may be administered thrice daily in the treatment of schizophrenia.

EXAMPLE 6

Oil extract	0.5 g
Methyl dihomog- γ -linolenate	10 mg

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Two capsules may be administered twice daily in the treatment of menstrual disorders.

EVIDENCE OF EFFICACY

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The conditions are considered in turn.

SCHIZOPHRENIA - Use of Oenothera Oil and Penicillin

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A female patient aged 24 who had suffered for 20 years from severe schizophrenia and was aggressive, paranoid and hypochondriacal in spite of conventional drug treatment with haloperidol (10 mg tds) plus flupenthixol decanoate (40 mg/month), was given Oenothera oil (2 x 0.6 ml capsules qds) and penicillin V (250 mg qds). There was some initial nausea and headache but after two weeks hypochondriacal delusions ceased and after six weeks paranoid delusions, aggressiveness and incongruity of affect had also disappeared. Further, 6 kg in weight were lost in the course of 16 weeks in spite of a regular

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diet.

A further, male patient of 31 had suffered from severe schizophrenic illness for 12 years and had been an in-patient for 7 years, aggressive, hearing voices, of wild staring appearance and not speaking spontaneously to others. He had been receiving fluphenazine decanoate 75 mg every two weeks, benzhexol 5 mg three times a day and supplementary chlorpromazine as required. He was taken off these drugs and given Oenothera oil and penicillin as above for one month and an increase to 3 capsules qds in the oil thereafter. Over a period of six months he became co-operative, not easily upset by fellow patients, without aggressions, speaking spontaneously and appropriately to others, and with almost normal affect. His ERPS score dropped from 44 to 21 over the period.

Four other severe chronic schizophrenics controlled by phenothiazines were withdrawn from them and given the Oenothera oil and penicillin. The condition of each was maintained without the side effects of the other drugs.

Use of Oenothera oil, Pencillin and Zinc

Preliminary trials with a small group of similar patients to those in the previous trials have been promising on the following:

Oenothera oil 6 or 8 x 0.6 ml capsules/day

Pencillin 250 mg qds

Zinc, as sulphate 20 to 40 mg/day

25 SKIN DISORDERS

Acne and psoriasis are two common and intractable conditions that have shown favourable results with treatment according to the invention.

A group of sufferers from severe acne, of 7 young men, received Oenothera oil 0.6 ml + zinc sulphate 20 mg, 6 capsules daily. All showed improvement in terms of reduction both in the number of inflamed facial pustules and in sebum production rate, over a period of 4 to 6 weeks.

After three months all the subjects showed a very substantial improvement, most being essentially clear of pustules.

A group of 4 subjects with psoriasis was given similar treatment. In all, scaliness and itching were reduced. In no case was there a full cure, but psoriasis is a particularly intractable condition in which even a modest improvement is clinically significant.

No clinical trials have been done on hair loss, but in a group of 30 laboratory rats maintained on a zinc deficient diet, hair loss was reversed by feeding of Oenothera oil with zinc, the effect being greater than when zinc was given alone.

Preliminary results with eczema using Oenothera oil and zinc together have given favourable indications, as found with psoriasis. Dandruff also responded favourably in two individuals otherwise wholly healthy.

OBESITY

Thirty-eight healthy subjects initially took Oenothera oil in 0.6 ml capsules for 6 - 8 weeks, thirty-four of them at 6 capsules a day and four at eight capsules a day, while continuing to eat their normal diets.

Twenty-two of the subjects, all taking 6 capsules a day, were initially within 10% of their ideal body weight according to the standard life tables. None gained or lost more than 2 kg.

The other sixteen subjects were all more than 10% above their ideal body weight. Of this group, two women and three men showed no change in weight. They were taking 6 capsules a day. Six women and five men lost weight, as follows:

Initial mean weight kg	74.55 \pm 7.94 (S.D.)
Final mean weight kg	70.42 \pm 6.52
	(p \pm 0.5, paired t test)

Of the subjects who lost weight, four who were taking 8 capsules a day lost 8.2, 10.0, 10.9 and 12.7 kg respectively. All the other subjects who lost weight were taking 6 capsules a day.

These results indicate that overweight individuals, but not those of normal weight, have a good chance of losing weight by simple inclusion of Oenothera oil in the diet, and that the weight loss is dose related.

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No adverse effects were observed. The intake of 6 capsules a day, 3.6 ml of the oil, is equivalent to ca 0.27 g of γ -linolenic acid, of 8 capsules a day, 4.8 ml of the oil, ca 0.36 g of γ -linolenic acid.

5 Preliminary results indicate improvement in terms of weight loss and proportion of subjects responding, when capsules containing 20 mg zinc sulphate in addition to the oil are used.

MENSTRUAL DISORDERS

10 A group of 15 women of reproductive age was treated, four of whom were using an intrauterine contraceptive device and all of whom were suffering from prolonged menstrus of 8 to 12 days with excess blood loss. Of these women, 5 also suffered from the premenstrual syndrome of depression, pain and fluid retention.

15 Initial administration of Oenothera oil 6 x 0.6 ml capsules daily over a period of several months consistently reduced the duration of blood loss to 3 to 5 days with concomitant reduction in the amount. The symptoms of the premenstrual syndrome in those women showing it became mild, or in one instance disappeared entirely and stayed gone for 3 full cycles, up to the end of the
20 trial.

Preliminary results indicate a further improved effect of oil capsules administered with 20 mg zinc sulphate.

USE OF ZINC

25 Substantial clinical results are not at present available on all the conditions for which the use of zinc is proposed, but the present inventor believes, without wishing to be limited to the theory, that at the root of all the conditions lies a fault in prostaglandin metabolism whereby PG's of the 1 series are lacking or their balance with 2 series PG's is upset. From evidence such
30 as that listed below the inventor believes that zinc increases formation of 1 series PG's selectively, apparently by mediating the mobilisation from ester resource of dihomogamma-linolenic acid.

Thus zinc is indicated in all the conditions described herein, as favouring 1 series PG synthesis specifically from administered
35 γ -linolenic acid and related materials.

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In one group of experiments the test preparation was the isolated superior mesenteric vascular bed, taken from male rats as for example described in the Canadian J. Physiol Pharmacol 54:357, 1976. The perfusion flow rate was at a constant value between 3 to 4 ml/min., pressure 25 to 30 mm Hg, using Krebs bicarbonate buffer containing in mM 150 Na, 4.3 K, 1.0 Mg, 2.5 Ca, 1.7 phosphate, 25 bicarbonate and 11.1 glucose.

Prior to testing the basic vasoconstrictive effect of norepinephrine, as the bitartrate, in successive 10 ng amounts was established, as the amplitude of a transient rise of about 1 min in the perfusion pressure.

Zinc, as the sulphate, was then added to the perfusion buffer at successive concentrations and the norepinephrine response measured after 15 minutes at each.

The following results were obtained

<u>Zinc concentration</u> <u>(ug/ml)</u>	<u>Response as %</u> <u>of basic level</u>
0.1	112
0.2	118
0.4	130
0.8	138

In the presence of 50 ug/ml of indomethacin, a known blocking agent for PG synthesis, used with 10 ng/ml PGE 2 to give apparently normal vascular reactivity, the zinc had no effect on the norepinephrine response.

Similar tests with dihomog- γ -linolenic acid and PGE 1 gave respective rises up to a maximum of 130% of the basic response at 50 ng/ml of the acid and a maximum of 150% of the basic response at 2.8×10^{-11} M PG.

The results show that zinc gives responses like those of dihomog- γ -linolenic acid and of PGE 1, responses moreover which are not given when PG synthesis is blocked and PGE 2 supplied, and thus that conditions treated with γ -linolenic acid (and thus effectively with dihomog- γ -linolenic acid) may be enhanced in the direction of 1 series PG synthesis by the addition of zinc.

USE OF ANTIBIOTICS

On tests carried out as above, both penicillin V and penicillin G have given responses similar in kind and degree to those given for zinc, supporting further the inventor's believe that β -lactam antibiotics are of value in all other conditions treated according to the invention, in similar way to the action of zinc, and as evidenced in the results on schizophrenia.

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CLAIMS

1. A pharmaceutical or dietary composition comprising (a) γ -linolenic acid or physiologically functional derivative thereof and/or dihomogamma-linolenic acid or physiologically functional derivative thereof and a conjoint amount of (b) physiologically
5 assimilable zinc and/or (c) a β -lactam antibiotic, alone or in an acceptable pharmaceutical or dietary vehicle.
2. The composition of claim 1, presented for administration in doses comprising 0.05 to 10 g of (a) calculated as linolenic acid and 2.5 to 800 mg of (b) calculated as zinc, or one half one third
10 or one quarter of said amounts.
3. The composition of claim 1, presented for administration in doses comprising 0.1 to 5 g of (a) calculated as linolenic acid and 10 to 200 mg of (b) calculated as zinc or one half one third or one quarter of said amounts.
- 15 4. The composition of claim 1, presented for administration in doses comprising 0.1 to 2 g of (a) calculated as linolenic acid and 10 to 200 mg of (b) calculated as zinc, or one half one third or one quarter of said amounts.
5. The composition of claim 1, presented for administration in
20 doses comprising 0.1 to 1 g of (a) calculated as linolenic acid and 10 to 200 mg of (b) calculated as zinc, or one half one third or one quarter of said amounts.
6. The composition of claim 3, 4 or 5, wherein the amount of (b) is 10 to 80 mg.
- 25 7. The composition of claim 1, wherein the antibiotic is a natural or semi-synthetic penicillin or cephalosporin antibiotic.
8. The composition of claim 7, wherein the antibiotic is selected from penicillin G, penicillin N, penicillin V, cephalothin, ampicillin, amoxycillin, cloxacillin, cephalexin and cephalogylcin.
- 30 9. The composition of claim 7 or 8, presented for administration in doses comprising 0.05 to 10 g of (a) calculated as linolenic acid and 0.5 to 3 g of (c), or one half one third or one quarter of said amounts.

10. The composition of claim 7 or 8, presented for administration in doses comprising 0.1 to 5 g of (a) calculated as linolenic acid and 0.5 to 3 g of (c), or one half one third or one quarter of said amounts.
- 5 11. The composition of claim 7 or 8, presented for administration in doses comprising 0.1 to 2 g of (a) calculated as linolenic acid and 0.5 to 3 g of (c), or one half one third or one quarter of said amounts.
- 10 12. The composition of claim 7 or 8, presented for administration in doses comprising 0.1 to 1 g of (a) calculated as linolenic acid and 0.5 to 3 g of (c), or one half one third or one quarter of said amounts.
13. The composition of any one of claims 7 to 12, containing the amounts of (b) set out in any one of claims 2 to 6.
- 15 14. A composition according to any preceding claim, wherein the physiologically functional derivative of γ -linolenic acid or dihomogamma-linolenic acid is a methyl or ethyl ester or glyceride thereof.
- 20 15. A composition according to any one of claims 1 to 13 wherein the γ -linolenic acid is present in the form of the oil of the seed of *Oenothera biennis* L, *Oenothera lamarckiana*, or other Evening Primrose species, or a fraction thereof.
- 25 16. A composition according to any one of claims 1 to 13, wherein the γ -linolenic acid is present in the form of the oil of the seed of *Borago officinalis* or other Borage species, or a fraction thereof.
- 30 17. A composition according to any preceding claim specifying the presence of zinc, wherein the zinc is present as a salt of a mineral or organic acid (and in particular zinc oleate, zinc γ -linolenate or zinc dihomogamma-linolenate), zinc oxide, or chelated zinc.
18. A composition according to any preceding claim, comprising further an effective and pharmaceutically acceptable amount of α -tocopherol or other antioxidant.
- 35 19. A pharmaceutical or dietary pack comprising (a) and (b) and/or (c) as set out in any one of claims 1, 7, 8 and 14 to 17, presented

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separately or two together and one separately but for conjoint administration.

20. A pack according to claim 19 wherein (a) and (b) and/or (c) are presented for administration in the relative amounts set out in the respective claim(s) of claims 2 to 6 and 9 to 12.

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EUROPEAN SEARCH REPORT

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Application number

EP 79 30 0079

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	FR - A - 2 272 684 (ITO SHOJIRO) * Claims 1-7 *	1,7- 16,20	A 61 K 33/30 31/43 31/545// (A 61 K 33/30 31/43 31/20 31/23 31/545)// (A 61 K 31/43 31/20 31/19 31/23 31/315)// ./.
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			A 61 K 33/30 31/43 31/545
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure F: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			Δ: member of the same patent family. corresponding document
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 12-03-1979	Examiner BRINKMANN

EUROPEAN SEARCH REPORT.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
			(A 61 K 31/545 31/20 31/19 31/23 31/315)
			TECHNICAL FIELDS SEARCHED (Int. Cl.)

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